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DOI:

[10.1016/j.rbmo.2017.06.007](https://doi.org/10.1016/j.rbmo.2017.06.007)

Document Version

Peer reviewed version

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Citation for published version (APA):

Palacios-González, C. (2017). Chimeras intended for human gamete production: an ethical alternative? *REPRODUCTIVE BIOMEDICINE ONLINE*. <https://doi.org/10.1016/j.rbmo.2017.06.007>

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Chimeras intended for human gamete production: an ethical alternative?

Abstract

Human eggs for basic, fertility and stem-cell research are in short supply. Many experiments that require their use cannot be carried out at present, and, therefore, the benefits that could emerge from these are either delayed or never materialise. This state of affairs is problematic for scientists and patients worldwide, and it is a matter that needs our attention. Recent advances in chimera research have opened the possibility of creating human/non-human animal chimeras intended for human gamete production (chimeras-IHGP). In this paper, I examine four arguments against the creation of such chimeras and prove that all of them are found wanting. I conclude by showing that there is a strong moral reason for scientists to pursue this research avenue.

Introduction

Different strategies have been proposed for increasing the supply of human eggs for research purposes: compensating women for egg donation, obtaining human eggs from aborted fetuses, posthumous egg donation, and in-vitro gametogenesis. Serious research efforts are dedicated to in-vitro gametogenesis at the moment (Hendriks et al., 2015). Each of these options, however, is faced with different ethical dilemmas and regulatory constraints (Baylis, 2009; Ellison and Meliker, 2011; Greely, 2016).

One possible avenue for solving the egg shortage problem is to create human/non-human animal chimeras intended for human gamete production (chimeras-IHGP). One way in which this can be achieved is through interspecies blastocyst complementation. In this technique, a non-human animal blastocyst is obtained from a mutant strain in which 'a gene critical for the development of a particular lineage is disabled' (Wuet al., 2016, 2017). Afterwards, this blastocyst is complemented with human stem cells, which will compensate for the existing niche.

Despite ongoing research and scientific and ethical discussions about the development of chimeras capable of producing solid organs, such as kidneys and hearts for transplantation

purposes, no wide discussion of the possibility of creating chimeras-IHGP has taken place. Scientists have only discussed how to avoid creating chimeras capable of producing human gametes (Rashid et al., 2014). A possible explanation for this is that many scientists consider that developing such chimeras is so ‘ethically and politically problematic’, that it is not even worth discussing this option. For example, Rashid et al. (2014), while discussing interspecies complementation for organ generation, have stated that:

[We are] sensitive to the fact that research with the potential to present the following hypothetical scenarios warrants particularly thorough consideration prior to commencement. (. . .) (2) Situations wherein functional human gametes (eggs or sperm) might develop from precursor cell types in an animal, and where fertilization between either human (or human-derived) gametes and animal gametes might then occur. (Rashid et al., 2014, p. 408)

In order to avoid the above, scientists are developing methods of target-organ generation that would preclude the accidental generation of human gametes within human/non-human animal chimeras (Kobayashi et al., 2015; Rashid et al., 2014). Owing to space constraints in this paper, I only discuss creating chimeras-IHGP for obtaining human gametes for research purposes. The ethical issues concerning use of chimera-generated human gametes for reproductive purposes, just as with in-vitro generated gametes for reproductive purposes, are important and need further exploration. For an up-to-date review of the scientific state of in-vitro gametogenesis, see Hendriks et al. (2015); for an up-to-date review of the ethics debate on in-vitro gametogenesis, see Smajdor and Cutas (2015) and Segers et al. (2017).

At this point, we must ask: why might developing chimeras-IHGP be so morally problematic that it should not be attempted? Four arguments against the creation of chimeras IHGP seem promising: human dignity would be violated by their creation; the value of human gametes would be debased by being generated within chimeras; generating such creatures is problematic because a human, or hybrid, pregnancy could ensue; and the research benefits of using such gametes do not outweigh the harms (death or pain) that the chimera would suffer. In what follows, I assess these arguments and show that they are found wanting, and then present an argument in favour of creating such type of chimera.

Human Dignity

Appeals to human dignity when objecting to new biomedical research are common. It,

therefore, seems natural that some may claim that the creation of chimeras-IHGP would constitute a violation of human dignity, and consequently that such creatures should not be created. The problem with this position is that it is not at all clear how human dignity could be violated by the mere creation of such creatures, as the claim that the creation of any human/non-human animal chimera (of which chimeras-IHGP are a subset) inherently violates human dignity is just false. We do not consider that the existence of a NOG mouse with engrafted human cells violates human dignity, even when it is a human/mouse chimera. Neither, do we consider that human dignity is violated when someone receives a pig heart valve, which effectively turns them into a chimera.

A more charitable reading of this kind of argument would rest upon the claim that creating a chimera-IHGP would create a being with human dignity. Therefore, it may be claimed that given this, and the belief that creatures in possession of a dignity ought not be used merely as a means to an end, chimeras IHGP should not be created. If this is what it is meant, then what would actually follow is that how we treat such creatures determines whether their dignity is violated, or not (Palacios-González, 2015a). From this position, it would also follow that we have the same moral obligations towards such chimeras as we have towards other human persons. If human dignity is tied to the possession of certain higher mental capacities, then as long as the chimeras-IHGP lack them, there would be no danger of violating their human dignity, as they would not possess it in the first place. Precluding the generation of human brain cells through genetic engineering, a strategy examined by Rashid et al. (2014), when creating chimeras-IHGP would highly reduce the possibility of accidentally creating a chimera with human brain cells. Therefore, as long as the chimeras-IHGP that we create do not possess higher mental capacities, it is simply not true that creatures with human dignity would be created, and even less that human dignity would be violated.

The value of human gametes

It may also be argued that chimeras-IHGP ought not be created because to do so would debase the value of human gametes. In order to answer this question, we first need to specify the kind of value that human gametes possess. Human gametes could possess two different types of value: inherent value or instrumental value. This means that they could be valuable in themselves or that they could be valuable as a means to achieve others' ends (Palacios-González, 2015b).

To defend the proposition that human gametes have intrinsic value is to assert that they have interests, that we have obligations towards them, and that the obligations we have towards them are based, at least partly, on their interests (DeGrazia, 2008). This position is implausible. What interests could a gamete have? To create an embryo? And if this were so, are we morally required to help gametes create embryos so they can fulfil their interests?

If it is held that human gametes do not have intrinsic value, they may still possess instrumental value. This means that they can have value as tools that we could use to achieve other ends. For example, most people resorting to IVF value their gametes not for themselves but as means to create a child. If it is true that human gametes only possess instrumental value then we have to ask if the value of chimera generated human gametes should be considered inferior to that of human-generated human gametes. The answer to this question, however, does not seem likely to be positive. Given that instrumental value is task-dependent, we have to assert that the instrumental value of chimera-generated human gametes should be assessed by examining how they perform as tools for achieving a certain goal. It is in relation to their capacity to achieve certain ends that we should judge them as valuable or not. For example, the instrumental value of chimera-generated human gametes for human embryonic stem-cell research should be assessed by establishing if they achieve the purpose intended by the researchers.

Given that (a) human gametes do not possess intrinsic value (that could be debased) and that (b) they can only possess instrumental value (which is task-dependent), we must conclude that the debasement of value argument is found wanting and thus fails to provide moral reasons for not creating chimeras-IHGP

Chimera human pregnancy

A third argument against the creation of chimeras-IHGP is that generating them is morally problematic because a human, or hybrid, pregnancy could ensue. Even if we accept, for the sake of argument, that we should not attempt, or allow, for chimeras to become pregnant with a human conceptus, it does not follow from this that we should not create chimeras-IHGP. This argument depends on the likelihood of a human or hybrid pregnancy ensuing, and this is a practical issue that can be easily dealt with. Henry T. Greely (2013) has proposed five courses of action to avoid these scenarios: creating chimeras of only one sex; using chimeras that are reproductively immature and euthanizing them before they reach reproductive maturity; sterilizing them; euthanizing them if they become pregnant; physically segregating them by

sex.

If our intention is to create chimeras-IHGP for their human eggs, then the first course of action seems the most appropriate in order to avoid ‘human pregnancies’: we should only create female chimeras. This would be the most sensible thing to do given that there is no shortage of human sperm for research purposes. In a scenario in which it is desirable to create chimeras capable of producing both female and male human gametes, we could just take the appropriate measures for them to be segregated by sex. As long as we are reliably capable of avoiding human or hybrid pregnancies the strength of this argument is insufficient for ruling out the creation of chimeras-IHGP.

Animal welfare

A final argument against the creation, and use, of chimeras-IHGP is that the harms that they would be subject to would not be outweighed by the benefits that they would produce; and given that nonexistence is not a harm, then we should not create them. In order to address this argument, we must first emphasise that the chimeras that we are considering here possess animal-proper mental capacities: meaning that they would possess the mental capacities of the non-human component. For example, a mouse-human chimera capable of producing human eggs would possess mental capacities that are species-typical for mice. This is important if we consider that the moral value of human persons, and thus the protections against unwanted harmful interventions, is related to their possession of higher cognitive capacities (Palacios-González, 2016).

It is true that certain research aims morally justify causing pain, or terminating, certain non-person sentient animals (e.g. mice). It is also true that other research aims fall short of justifying such harms (e.g. developing a new cosmetic eyelash). Also, it is uncontroversial that saving people’s lives, or ameliorating people’s great suffering, are aims that justify harming or killing certain sentient animals, when there are not other means available to us. Therefore, if the research aims for using chimeras-IHGP are geared towards saving people’s lives, or ameliorating people’s great suffering, then creating them and later on extracting their human eggs is morally justifiable. On the other hand, the moral permissibility of using chimeras-IHGP in research that is not geared towards saving people’s lives, or ameliorating people’s great suffering, will depend, partially, on the fact if the harms imposed are proportional to the expected net benefits (DeGrazia and Sebo, 2015). Discussing, specifically, if it is morally

permissible to create human/non-human primate chimeras for generating human gametes would require much more space than available; see Shaw et al. (2014), Palacios-González (2016), and Dondorp et al. (2016) for a recent debate on the creation and use of human/non-human primate chimeras.

Two important caveats must be mentioned. First, we should extract the chimera's eggs in the least harmful way possible. Second, if other morally permissible methods were available for obtaining human eggs (e.g. in-vitro gametogenesis) that would not require creating and experimenting on sentient creatures, then we should choose those other means. Given the urgency of the human egg shortage problem, at this point in time we should simultaneously explore the chimera route and the in-vitro one, and only give up the former route if the latter one, or another one, is capable of adequately dealing with the human egg shortage problem.

We can confidently assert that the animal welfare argument is not successful in presenting a principled argument against creating, and using chimeras-IHGP if other forms of research which involve causing harm to non-human animals for the purpose of saving the lives of or ameliorating the suffering of people are considered permissible. Indeed, given that research aimed at saving people's lives or ameliorating the great suffering of people is generally deemed not only permissible but morally urgent, we can assert that there may in fact be strong moral reasons to pursue research into chimeras-IHGP. Even when it is true that the force of this positive argument depends on the utility of chimera-produced human gametes, and thus it is open to empirical verification, we cannot rule out in principle this research avenue.

Conclusion

In conclusion, I have questioned in this paper the morality of a chimera solution to the human egg shortage problem. I examined four possible arguments against this option and showed that all of them are found wanting. The first concerned the claim that human dignity would be violated by the creation of chimeras-IHGP. This argument fails because what would follow, if true, is that a creature with dignity would be created. I also pointed out that given that most chimeras-IHGP would not possess higher mental capacities then they would not possess human dignity in the first place. The second suggested that the value of human gametes would be debased and that we should therefore not proceed down this path. This argument also fails because human gametes, either generated by humans or chimeras, do not possess intrinsic worth capable of being debased. Human gametes only possess instrumental value and this value

is task-dependent. Third, arguments suggesting that the possibility of a human or hybrid pregnancy in fact requires from us not to create such chimeras were considered. These were also determined to fail because we can easily and effectively prevent such pregnancies from happening by, for example, only creating female chimeras. Lastly, the claim that the aims of such experiments do not morally justify creating and using such chimeras was explored. It was found, however, that this argument cannot successfully ground a principled case against creating and using chimeras-IHGP, because there are certain aims that morally justify harming sentient animals, for example saving a person's life.

Finally, it was noted that there is a strong moral reason to create and use chimeras-IHGP: forwarding research capable of saving people's lives and ameliorating people's great suffering. Scientists should accept that there is nothing particularly morally problematic with creating chimeras-IHGP and should start actively looking into this direction. For a previous in depth exploration of the philosophical topics concerning the creation of chimeras-IHGP see Palacios-González (2015b).

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